Increased level of bronchial responsiveness in inactive children with asthma

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Abstract We estimated the association between bronchial responsiveness and hours of exercise per week in children with and without asthma. A random sample of school children (n = 2188), 6–16 years old, was enrolled in a cross-sectional study of asthma in Oslo using the ISAAC questionnaire. Lung function and bronchial responsiveness (BR) using methacholine was measured in a random sample of 80 children with asthma, wheeze and no asthma/no wheeze. The relation between hours of exercise per week and BR [log (DRS)] was estimated by linear regression. Sex and age were included as covariates. Hours of exercise were categorized in: none, 30 min, 1 h, 2–3 h, 4–6 h and 7 h or more. The mean values of log (DRS) were different in the low and high exercise groups for children with asthma (P = 0·02), whereas there was no effect of exercise on BR for children without asthma. BR increased with decreasing hours of exercise per week in children with asthma. The bronchial responsiveness decreased with 0·11 (95% CI −0·20, −0·01) pr unit in scale. This pattern was not present in children without asthma. The results suggest that there is a relation between hours of exercise per week and bronchial responsiveness in children with asthma.

doi:10.1053/rmed.2001.1149, available online at http://www.idealibrary.com on IDEAL®

Keywords childhood asthma; bronchial responsiveness; physical activity.

INTRODUCTION

A higher prevalence of asthma and increased bronchial responsiveness are reported among elite athletes compared to the general population (1–4). There are reports of an increased bronchial responsiveness among swimmers during intense training and in cross-country skiers during the winter season (5,6). Increased airway exposure to chlorine and cold air was proposed as explanatory factors. The inflammatory process of the airways of skiers with asthma may differ in degree or nature from that seen in usual asthma (7). In addition, the findings of a study among Norwegian elite athletes suggest that the aetiology of asthma among athletes may be related to extensive training (8). The results of these studies indicate that exercise could affect the development of asthma and increased bronchial responsiveness among highly physical active individuals. Furthermore, the findings suggest that the occurrence of asthma and increased bronchial responsiveness may in part be triggered by an exercise–environment interaction.

Received 3 July 2000 and accepted in revised form 11 June 2001
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Evidence for an association between inactivity and the occurrence of asthma and bronchial responsiveness is sparse (9–11). Inactivity or obesity associated with inactivity may be associated with diminished tidal lung expansion, inhibiting lung mechanical forces tending to protect the airway from collapse (9). This may result in static or dynamic reduced airway calibre as well as restrictive physiology. A cross-sectional study from Taiwan found that body mass index (BMI) was associated with allergic sensitization and hay fever as well as increased bronchial responsiveness (BR) (12). A Danish study found that among 757 previously asymptomatic children followed from 1985 to 1996, those who developed asthma at follow-up had lower mean physical fitness (11).

Asthma represents the clinical manifestation of a number of different pathogenic processes, and a general liability to develop the disorder, may be differentially expressed in individuals. One can assume that this liability is comprised of many genetic and environmental influences and is normally distributed within the population (13). Exercise is known to induce a cascade of physiological responses, which may vary dependent upon the type, intensity and duration of exercise (14,15). Thus, level of exercise could affect the airways and influence the development of BR. Furthermore, it is likely that exercise may

differentially affect the level of bronchial responsiveness in individuals with and without an increased liability to develop bronchial hyper-responsiveness.

The aim of the present study was to assess the association between bronchial responsiveness and hours of exercise per week in children with and without asthma.

METHODS

In January 1994, a random sample of school children ($n = 2188$), 6–16 years old, was enrolled in a cross-sectional study of asthma and allergy in Oslo using the ISAAC questionnaire (16,17). Other questions previously used in studies of childhood asthma were included (16). The children were classified into three groups based on the responses to the questionnaire, children with current asthma, non-asthmatic children with wheeze and children with no asthma and no wheeze (18). 'Asthma' was defined by a positive response to both of the following two questions: 'Has the child ever had asthma?' and 'Does the child still have asthma?' 'Wheeze' was defined by a positive answer to the question, 'Has the child had wheezing or whistling in the chest in the last 12 months?' and a negative answer to the question, 'Has the child ever had asthma?'. 'No asthma/no wheeze' was defined by a negative response both to the asthma question and to the question on wheezing or whistling in the chest in the last 12 months. The study population and methods have been previously described elsewhere (16–18).

A total of 5·5% (121/2188) of the children had current asthma, 6·3% (138/2188) were non-asthmatic children, who reported wheeze or whistling in the chest in the last 12 months and 88.2% (1929/2188) reported neither asthma nor wheeze (18). A random sample of 80 children from each group was drawn to take part in a clinical examination of lung function and bronchial responsiveness (BR) (18). The testing procedures have been previously described in detail (18). Children with wheeze and no asthma/no wheeze were similar with respect to several parameters such as bronchial responsiveness and atopy using skin prick test, and they are therefore included as one group in the present analysis (18).

Exercise

The physical activity level was assessed by using two questions of physical activity level from the WHO Cross-National Survey Of Health Behaviour In School-Aged Children (19). Here, hours of exercise was based on the following question: 'Outside of school hours: how many hours a week does the child usually exercise in the free time so much that he/she becomes breathless or sweats?' Six categories were ranged from 'none' to '7 h or more'. In the present analysis, exercise hours per week were divided into two categories: 0–3 h and $\geq$ 4 h, and then the adjusted degree of bronchial responsiveness was calculated per unit in scale (using all six categories).

Testing procedures

Children using short-acting β_2-agonists were asked to withhold medication 8 h before examination, theophylline 12 h, theophylline depot 72 h, β_2-agonist tablets or mixture 12 h and anti-histamines for 1 week. Participants had to be free from respiratory infections for 6 weeks before testing. Other criteria for not being tested were symptoms of bronchial obstruction, forced expiratory volume in 1 sec (FEV_1) less than 60% of predicted value, and smoking within 12 h before testing. Testing had to be postponed until the criteria were fulfilled. Two subjects did not fulfill the criteria.

Lung function tests

Lung function was measured by maximum forced expiratory flow–volume curves (Master Lab., Erik Jaeger, GmbH and Co. KG, Wurzburg, Germany). Calibration was performed daily. The measurements were obtained with the child sitting wearing a nose clip. Children practiced the technique until they achieved a representative maximum forced expiratory curve with variability less than 5% between two tests. The highest FEV_1 value was used in the analyses. Predicted values of FEV_1 were based on reference values according to Zapletal (20).

Bronchial responsiveness using a challenge of methacholine

A methacholine bronchial challenge test was performed using standard methods (21). Baseline lung function was measured, and a dose of saline was administered as a control. Baseline lung function was measured again and used as the reference value. Methacholine was administered by an aerosol provocation system with a fixed output (APS Jaeger, Erik Jaeger) in doubling doses ranging from 0·128 to 16·3 μmol. Each nebulization was triggered by inspiration, lasted 0·5 sec and yielded an output of 0·5 ml. Lung function was measured 1 min after each dose. The test was stopped if FEV_1 fell 20% or more from the post–saline (control) value, or when all methacholine dose steps to 16·3 μmol had been administered. Inhalation of salbutamol was administered to aid recovery when necessary.

Dose–response slope (DRS)

For all children the response to the methacholine challenge was expressed as the dose–response slope (DRS) (21). The dose–response data of each child were calculated as the percentage fall in FEV_1 from the post-saline

value of FEV_1 after the last methacholine dose, divided by the total cumulative dose (21). The values of DRS in the present paper are indicated by units of per cent fall in FEV_1 μmol^{-1}. Nine subjects with a value of zero or less (range: 0·13–0) were given the value 0·01. Lastly, the DRS measure was log-transformed.

Statistical analyses

In the unadjusted analysis we compared mean log (DRS) in the low and high exercise groups for children with and without asthma. In the adjusted analysis the relations between bronchial responsiveness [log (DRS)] and hours of exercise per week for children with and without asthma were estimated by linear regression (22). Hours of exercise, sex, age, asthma and an interaction term between exercise and asthma were included as covariates. After fitting the model we performed a selection of standard regression diagnostics. Studentized deleted (jackknife) residuals were plotted against predicted values to check for non-constant error variance (heteroscedasticity) and for non-linear trends. We also plotted the same residuals against each covariate to look for non-linear trends. The Cooks distances were plotted against observation number to look for observations with large influence. We also plotted $\delta - \beta$ of hours of exercise against observation number to look specifically at the robustness of this estimate.

RESULTS

The number of boys was higher in the asthma group compared to the other groups, but the groups were comparable with respect to age, height, weight and baseline lung function (Table 1) (18).

The distributions of DRS were almost identical for the wheeze and the no asthma/no wheeze groups (18), whereas it was different for the asthma group, where the slopes were steeper for a greater percentage of the children. The median DRS was 5·54 (% fall in FEV_1 μmol^{-1}) in the asthma group, 0·75 in the wheeze and 0·89 in the no asthma/no wheeze group (18).

Twelve per cent children with asthma exercised less than one 1 h per week compared to 10% without asthma. Respectively, 38% and 35% exercised 4–6 h per week.

The mean values of log (DRS) were different in the low and high exercise groups for children with asthma ($P = 0·02$, Table 2), whereas there was no effect of exercise on bronchial responsiveness for children without asthma.

Linear regression analysis showed that bronchial responsiveness increased with decreasing hours of exercise per week in children with asthma, log (DRS) decreased with a value of 0·11 (−0·20, −0·01) for each unit decrease in exercise (Table 2). This pattern was not present in children without asthma (Table 2).

The regression diagnostic plots showed no indication of heteroscedasticity or of non-linear trends, and there were no observations with very high influence, i.e. the estimated risk differences were robust.

DISCUSSION

In our cross-sectional study an increased level of bronchial responsiveness (BR) was present in children with current asthma with the lowest level of physical activity, whereas this relation was not present in children without asthma.

The present cross-sectional design has limitations for making causal inferences. The results may indicate that severe disease lead to inactivity or that inactivity result in increased level of BR. Increased level of BR may, however, not reflect asthma severity (15,23). We emphasize that our findings need to be examined in a longitudinal study following children from early childhood where

Table 1. The characteristics of children with current asthma, wheeze without asthma (wheeze) and no asthma/no wheeze. Age, height, weight, and baseline lung function (FEV_1) are in mean values with 95% confidence interval (CI)

	Asthma n=78		Wheeze n=70		No asthma/no wheeze n=76	
	n	%	n	%	n	%
Boys	52	67	30	43	34	45
	Mean	(95% CI)	Mean	(95% CI)	Mean	(95% CI)
Age (years)	10·3	(9·8–10·8)	10·6	(10·1–11·2)	10·6	(10·0–11·1)
Height (cm)	153	(140–156)	157	(153–160)	154	(151–157)
Weight (kg)	43·9	(40·8–46·9)	47·0	(43·6–50·4)	44·2	(41·4–47·1)
FEV_1 ($l\,sec^{-1}$)	2·48	(2·29–2·68)	2·71	(2·50–2·92)	2·66	(2·48–2·84)

Table 2. The association between exercise hours per week and bronchial responsiveness in children with and without asthma

	Bronchial responsiveness			
	Unadjusted*		Adjusted	
	Mean log(DRS)	*P*-value	RD	95% CI
Children with asthma				
Exercise hours per week				
0–3 h	1·1	0·02		
≥ 4	0·75			
Pr unit in scale			−0·11	(−0·20, −0·01)
Children without asthma				
Exercise hours per week				
0–3 h	0·45	0·8		
≥4 h	0·44			
Pr unit in scale			0·00	(−0·07, 0·08)

*Adjusted for age and gender.

physical activity level continuously has to be assessed. In the assessment of physical activity there is a question of reliability and validity. The results in the present study were based on parental reports of participation in sports and physical activity in their children, which may be influenced by misclassification. Self- or parental reports of physical activity do not reflect the real level of physical activity. Validation studies have shown that the level of physical activity may be over-estimated (24). The purpose of the present study was, however, to provide descriptive information of data and conduct simple analysis of differences between groups. It is unlikely that parents of children with and without asthma should recall differently the physical activity level of their children. Similar questions have been used in many studies, and it may be useful in discriminating between inactive and active children (24). Other factors that may influence our results are initial lung function, virus infections, smoking or exposure to other pollutants and allergen exposure. It has been found that reduced starting lung function can be a small but significant independent determinant of the level of BR (25). However, initial level of lung function was part of the model. It is also unlikely that virus infections, smoking or other pollutants and allergen exposure should affect our results. Children with respiratory tract infections were not tested. Smoking in this age group is rare. The exposure of other pollutants and allergens should also be equally distributed, and the level of air pollution is low in the areas where these children are living (26).

A relation between BR and hours of exercise per week in athletes may be associated with the exposure of the airways to thermal and osmotic stimuli (27). Exercise may result in a repeated over-stimulation of the mechanisms that protect against dry air-induced mucosal injury (27). If such injury occurs, it may lead to chronic inflammation. Repeated exposures to dry air may then contribute to the pathogenesis of BR. Periods of excessive amounts of exercise may also confer a greater than normal risk for upper respiratory tract infection (28–30). Consequently, recurrent infections in addition to exercise may contribute to the development of increased BR. High levels of exercise also increase the exposure of the airways to environmental factors such as air pollutants and allergens that could increase the risk of developing increased BR.

The relation between inactivity and increased level of BR is less explored. In the Danish study there was a weak association between physical fitness in 1985 and BHR in 1996 when controlled for sex, age and BMI (11). Another study has reported positive association between BMI and childhood asthma, but not allergy (10). Whether the cascade of physiological responses due to exercise influence BR alone, or is influenced by other life style factors associated with an inactive life style such as weight gain and eating habits need further investigation. One plausible explanation is that the association between inactivity and increased BR is related to a higher percentage of body fat among inactive children. Adipocytes produce proinflammatory cytocines such as necrosis factor (TNF) α as well as interleukin (IL)-6 (31). IL-6, when produced by the mast cell in the lung, contributes to the late-phase asthmatic response (32). Skin-fold measures was not included in our study. A study that examined the role of physical activity, inactivity and dietary patterns on annual weight gain found that a 1-year increase in BMI was larger in those who reported more time with TV, videos and games (33). A larger increase was also seen among less physical active girls who reported higher caloric intake (33).

It is becoming increasingly clear that asthma falls into the category of complex diseases, for which the development is determined by the interaction between host susceptibility and environmental exposures (34,35). Children with asthma may reflect a sub-population with increased liability to develop BR. They may respond differently to inactivity and a possible exercise–environment interaction compared to normal children. In conclusion, the results suggest that there is a relation between exercise and bronchial responsiveness in children with asthma. A possible relation between inactivity and asthma need further investigation.

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